IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES, LLC, FOREST LABORATORIES HOLDINGS, LTD., MERCK KGaA and MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG, Plaintiffs, v. ACCORD HEALTHCARE INC., et al., Defendants.	C.A. No. 15-272 (GMS) CONSOLIDATED

DECLARATION OF JOEL BERNSTEIN, Ph.D., IN SUPPORT OF PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

I. INTRODUCTION

I, Joel Bernstein, Ph.D., declare and state:

1. I have been retained by Plaintiffs Forest Laboratories, LLC and Forest Laboratories Holdings, Ltd. ("Forest") and Merck KGaA and Merck Patent Gesellschaft mit beschränkter Haftung ("Merck") (collectively, "Plaintiffs") in connection with the above-referenced matter as a technical expert on the subject of polymorphism of pharmaceuticals and solid state organic chemistry.

2. I understand that Plaintiffs allege that defendants Accord Healthcare, Inc. ("Accord"), Alembic Global Holding SA, Alembic Pharmaceuticals Inc., and Alembic Pharmaceuticals Ltd. (collectively, "Alembic"), Apotex Inc. and Apotex Corp. (collectively, "Apotex"), Teva Pharmaceuticals USA, Inc. ("Teva"), and InvaGen Pharmaceuticals Inc. ("InvaGen") (collectively, "Defendants") have infringed U.S. Patent Nos. 7,834,020 (the "'020 patent"), 8,193,195 (the "'195 patent"), 8,236,804 (the "'804 patent"), and 8,673,921 (the "'921

patent") (collectively, "patents-in-suit"), by filing Abbreviated New Drug Application ("ANDA") Nos. 208209, 208202, 208228, 208212, and 208200, respectively, seeking FDA approval to make and sell a generic version of Forest's VIIBRYD® product prior to the expiration of the "patents-in-suit."

3. I understand that the parties in this case will be asking the Court to define certain terms contained in the patents-in-suit in a process I understand is referred to as "claim construction." I have been asked by Plaintiffs to provide an explanation, for the benefit of the Court, to provide some technical background regarding polymorphism. I have also been asked to explain how certain terms appearing in the claims of the patents-in-suit would have been understood by a person of ordinary skill in the art with respect to the patents-in-suit as of June 2001, as set forth below.

II. QUALIFICATIONS

4. The opinions below are based on my background and experience including my forty-nine (49) years of professional and educational experience in the study, characterization, and analysis of organic solids, as well as the documents cited herein.

5. My qualifications as an expert in these areas are established by my curriculum vitae, which is attached as Exhibit A, and the publications cited therein. I have set forth below representative relevant experience.

6. I received a B.A. degree in chemistry from Cornell University in 1962 and a M.Sc. degree and Ph.D. degree in chemistry from Yale University in 1967. Upon completing my Ph.D., I was a postdoctoral fellow for two years at the University of California in Los Angeles, and for two additional years at the Weizmann Institute of Science in Rehovot, Israel. During that time period (1967-1971), I specialized in the areas of organic solid state chemistry,

polymorphism, chemical crystallography, the properties of organic solids, and X-ray crystallography. Since 1967, I have used a variety of analytical techniques to study, characterize, and understand organic solids.

7. My appointment since September 1, 2013 is Global Distinguished Professor of Chemistry at New York University Abu Dhabi/Shanghai; for three years prior to that I was Professor of Chemistry at the same institution. Until my mandatory retirement in January 2010, I was a Professor of Chemistry and the incumbent of the Carol and Barry Kaye Chair in Applied Science at Ben-Gurion University of the Negev, Beer Sheva, Israel, where I had been a faculty member since 1971. During the course of my career, my research activity has dealt with the structure and properties of the organic solid state. I have employed a variety of analytical techniques to prepare, identify and characterize solid forms with an emphasis on the variety of solid forms possible, generally referred to as polymorphism. I have taught and continue to teach courses in general chemistry, crystallography, and organic solid state chemistry, including polymorphism and crystallization.

8. I have been and continue to be involved in professional organizations dealing with crystallography. I have twice been President of the Israel Crystallographic Society. I was founding Vice President of the European Crystallographic Association and Chairman of the Organizing Committee of the XIX Congress and General Assembly of the International Union of Crystallography held in 2002 in Geneva (with approximately 2,000 participants). I was a co-convener of the European Polymorphism Network, a consortium of European scientists active in all areas of polymorphism, which was founded in 2001 under the auspices of the European Science Foundation. In 1999, I was elected a Fellow of the American Association for the

Advancement of Science. I was co-director of the NATO International Advanced School on Polymorphs and Solvates, which took place in Sicily in June 2004.

9. In addition, I have engaged in industrial consulting in the areas of polymorphism of pharmaceuticals and solid state organic chemistry and crystallography for pharmaceutical companies such as Minnesota Mining and Manufacturing Co. (3M), GlaxoSmithKline PLC, Eli Lilly and Co., Pfizer, Inc., Abbott Laboratories, Astra Zeneca and Sanofi-Aventis Pharmaceuticals.

10. I have also published extensively on the topics of polymorphism, crystallography, and organic solid state chemistry, including refereed papers, book chapters and reviews. I authored a book entitled "Polymorphism in Molecular Crystals," published by Oxford University Press in 2002. Pages 6 through 26 of my curriculum vitae list my approximately 200 scientific publications, most of which deal with those topics.

11. I am frequently invited to speak at international meetings, symposia and advanced schools, and have held a number named guest lectureships and visiting professorships. I have received numerous honors for my work, including being elected a fellow of the American Association for the Advancement of Science in 1999. My other honors and professional affiliations are also listed in my CV.

III. MATERIALS CONSIDERED

12. In connection with the preparation and submission of this declaration, I reviewed the patents-in-suit and their prosecution histories, the parties' proposed claim constructions and Joint Claim Construction Charts, and the literature references cited herein.

IV. SUMMARY OF OPINIONS

13. Based on my review of the above materials, as well as my background and experience, I have formed the following opinions, which are set forth in more detail below.

14. A person of ordinary skill in the art ("POSA") would understand that the claim term "crystalline" has its plain and ordinary meaning, and that the claim term "crystalline modification" means "crystalline form."

15. A POSA would understand that the claim term "corresponding to" has its plain and ordinary meaning of "consistent with." A POSA would not understand this claim term to require XRD peaks to match the precise values in the claims.

16. A POSA would understand the claim term "exhibits the following XRD data" to mean "displays X-ray diffraction pattern consistent with the following values, with experimental error ranges (*e.g.*, +/- 0.1^{o} for two-theta values)." A POSA would not understand the claim term to allow for no experimental margin of error.

17. A POSA would understand that the term "characteristic peak" has its plain and ordinary meaning of "peak representative of a crystalline form's X-ray diffraction pattern." A POSA would not understand this claim term to require the peaks to have intensity $\geq$ 3*noise.

V. A PERSON OF ORDINARY SKILL IN THE ART

18. I understand that a patent is read, and the art evaluated, from the perspective of a person of ordinary skill in the art at the time of the relevant priority date (here, June 2001). It is my opinion that a person of ordinary skill in the art with respect to the patents-in-suits would have had at least a bachelor's degree in chemistry, pharmaceutical sciences or a related discipline, along with several years of experience working in pharmaceutical solid product development and/or solid state chemistry. A POSA also would have knowledge and experience,

and/or access to others with knowledge and experience, in treating patients for depression or other conditions identified in the patents-in-suit, and evaluating the effects of such treatment. Under this definition, I am at least a person of ordinary skill in the art, and was during the relevant time period.

VI. TECHNOLOGY BACKGROUND

A. Solid State Forms in Drug Products

19. Pharmaceutical tablets are composed of some solid state forms of the active pharmaceutical ingredient (API) together with excipients. Solid state forms include crystalline and amorphous forms. Crystalline solids have a regular arrangement of atoms or molecules that repeats in three dimensions, also referred to as three-dimensional long-range order. Crystalline solids can be identified experimentally, for instance by X-ray diffraction because they generate X-ray diffraction peaks, as discussed further below. *See, e.g.*, Hancock *et al*., J. Pharma. Sciences, 1997, vol 86, 1-12 (submitted herein as "Exhibit B"); and A Dictionary of Chemistry 140 (John Daintith Ed., 3rd ed. 1996) (submitted herein as "Exhibit C").

20. The arrangement of the constituent atoms or molecules in a crystalline solid is referred to as the crystal structure. The basic building block that is repeated in three dimensions to form the lattice is a mathematical construct called the unit cell. There is an intimate relationship between the structure of the solid and the physical and chemical properties of the material. For example, crystalline solids can provide high physical and chemical stability, and advantageous properties for pharmaceutical manufacturing and formulation.

21. Many substances are capable of crystallizing in more than one crystal structure—a phenomenon known as *polymorphism*. Some compounds also may crystallize in different solvated forms, which include water (known as a hydrate) or other solvents. Because of the

intimate relationship between a compound's structure and its properties, different crystalline forms of a compound can and often do exhibit different properties.

22. While many pharmaceutical compounds have been found to exist in a number of different crystalline forms, every compound provides a unique situation. When multiple crystalline forms of a compound exist, it is not possible to predict each form's properties, such as its relative stability, solubility, or its tendency to convert to another form. For example, although thermodynamic principles favor formation of the lowest energy form, kinetic factors may prevent this. In 2001, it was not possible to predict with any degree of confidence if a compound will exhibit multiple crystalline forms, let alone what such forms would be and what would be the properties of those forms. This remains true today. Nor can one prescribe in advance how to make possible (unknown) crystalline forms. In other words, until a particular form of a compound is discovered, there is no way to predict *a priori* that form, how to prepare it, or any of its properties.

B. Methods of Characterizing Crystalline Forms

23. A variety of techniques may be used to characterize crystalline forms. Representative techniques include X-ray diffraction (XRD), Raman spectroscopy, differential scanning calorimetry (DSC), infrared (IR) spectroscopy, nuclear magnetic resonance (NMR), and melting point determination. X-ray diffraction directly probes the solid state structure, and thus is a common technique for the identification of solid state forms.

24. X-ray irradiation of solids having long-range order results in the X-ray beams being scattered (diffracted) at specific angles. When the sample is a powder, the diffraction pattern is usually measured as the amount of scattering (intensity) on the y-axis as a function of the angle on the x-axis (2-theta), and peaks of varying intensity appear at specific 2-theta values

in an XRD pattern. Bragg's law describes the relationship of the scattering angles of the X-ray radiation to the spacings between planes of molecules in the crystal lattice. Bragg's Law is expressed as $n\lambda = 2d\sin\theta$, where λ is the wavelength of the X-ray radiation (usually measured in Ångstroms, Å), d is the distance between parallel planes in the crystal (in Å), n is an integer value representing the order of the diffraction pattern, and θ is the angle between the X-ray radiation hitting the sample and the parallel planes with spacing d. As noted above, the resulting X-ray diffraction pattern is a plot of the diffraction intensity (I) on the y-axis as a function of degrees two-theta (2θ) on the x-axis. The relative intensity ratio I/I_0 can be used to compare the intensity (I) of a given peak to the intensity of the largest peak (I_0) in the diffraction pattern.

25. The number of peaks in an XRD pattern and the size and shape of the peaks are a function of many factors, such as (but not limited to) the degree of crystallinity, mosaic spread, preferred orientation, measurement geometry and parameters, the local environment of the crystalline material, the concentration of the material present in a mixture, sample preparation, particle size, and crystal habit. The measured XRD pattern for a given sample can vary (even across samples of the same crystalline form of the same compound) based on the specific instrumentation and experimental conditions employed. Therefore, XRD data, like any other experimental data, necessarily will include some experimental margin of error.

26. Notwithstanding the many differences that can occur in XRD patterns, it is often possible to identify the presence of a compound in crystalline form from a peak or peaks that are characteristic of that crystalline form. These representative peaks allow for a given crystalline form of a compound to be distinguished from other materials. In fact, the XRD pattern of a solid material is often considered to be a fingerprint of that material. However, similar to the analysis of a forensic set of fingerprints, for the reasons indicated above, the absence of some peaks from

a set of characteristic peaks, or a change in intensity or relative intensity of the peaks, cannot be interpreted as indicating that the crystalline form is not present.

VII. THE PATENTS-IN-SUIT

27. The patents-in-suit describe the invention of crystalline forms of vilazodone hydrochloride, pharmaceutical compositions and methods of using the same. The solid form of an active compound that is developed into a pharmaceutical product must provide suitable stability, uniformity, and formulation properties. *See, e.g.*, '804 patent, col. 2, ll. 1-16.[1]

28. For example, the inventors noted that "if the morphological form is not held constant during clinical and stability studies, the exact dosage used or measured may not be comparable from one lot to the next." *See* '804 patent, col. 2, ll. 3-6. Additionally, "it is important to recognize the morphological form delivered in each dosage form to assure that the production process use[s] the same form and that the same amount of drug is included in each dosage." *See, id.*, col. 2, ll. 7-10.

29. The inventors succeeded in developing new morphological forms of vilazodone hydrochloride, including Forms I-XVI, and pharmaceutical formulations and methods of using the same. The inventors provided experimental data for these forms, including IR absorption spectra, X-ray diffractograms, thermal analysis diagrams, and Raman spectra. *See id.*, Figs. 1-46; col. 2, ll. 7-10; col. 21, l. 14 to col. 27, l. 11.

30. The inventors of the patents-in-suit surprisingly found that the newly-identified crystalline forms of vilazodone possess advantages over previously-prepared materials, including "reduced hygroscopicity, better compressibility during the [tableting] process, prolonged shelf life, better thermodynamic stability, i.e.[,] stability against heat and humidity, better resistance to

[1] I understand that all four of the patents-in-suits share the same specification. Thus, all references to the specification herein are made to the '804 patent as a representative example, and include corresponding cites in the '020, '195, and '921 patents.

sunlight, i.e.[,] UV-light, increased bulk density, improved solubility, bioavailability characteristics which are constant from one batch to the other, better flow and handling properties in the tableting process, improved color stability, better filtration properties in the production process." *See id.*, col. 5, ll. 1-18. The patents-in-suit also describe pharmaceutical compositions and methods of using the new vilazodone crystalline forms to treat conditions including depressive disorders. *See id.,* Abstract, col. 1, ll. 24-26 and 30-36; col. 2, l. 39 to col. 3, l. 30; col. 14, l. 60 to col. 16, l. 13.

VIII. CLAIM CONSTRUCTION

31. I understand that patent claims are interpreted from the perspective of a person of ordinary skill in the art at the time of the patent's relevant priority date (here, June 2001). I understand that claim terms generally are afforded their plain and ordinary meaning to a person of ordinary skill in the art, when read in view of the patent specification and prosecution history.

32. Based on my experience and the materials I reviewed, I set forth my opinions about how a person of ordinary skill in the art would understand the following disputed claim terms.

A. "Crystalline"/"crystalline modification"

Claim Term	Patent/claim	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"crystalline"	'195 patent, claim 1 '020 patent, claim 1 '921 patent, claims 1, 5, 11, 13 '804 patent, claim 1	Plain meaning/no construction required	Entirely in crystalline form comprising only Form I to XVI, and combinations thereof (as appropriate)
"crystalline modification"	'020 patent, claim 1 '921 patent, claims 1, 5, 11, 13 '804 patent, claim 1	Crystalline form	Construe together with "crystalline"

33. For instance, claim 1 of the '195 patent recites "[a] method of treating a depressive disorder, the method comprising: administering to a patient in need thereof an effective amount of a compound which is a *crystalline* hydrochloride salt of l-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine, wherein a depressive disorder is treated in the patient" (emphasis added).

34. In my opinion, a POSA would have understood "crystalline" as used in the claims of the patents-in-suit according to its plain and ordinary meaning.

35. "Crystalline" is a common and well-known term in the art of solid state chemistry. A POSA would understand that this term refers to a solid form in which atoms or molecules are arranged with a three-dimensional long-range order. *See, e.g.*, Hancock *et al.*, *supra* at 1; A Dictionary of Chemistry, *supra*, at 140.

36. The patents-in-suit use the term "crystalline" consistently with this common understanding. For example, the '804 patent describes new crystalline forms of vilazodone hydrochloride, their advantageous properties, and their use in treating various medical conditions. *See, e.g.*, '804 patent, col. 2, l. 39 to col. 3, l. 30; col. 5, ll. 1-22. Additionally, during patent prosecution, the term "crystalline" was used consistently with this common understanding. *See, e.g.*, File history of '921 patent, preliminary amendment filed September 19, 2013, at pp. 3-5; Notice of Allowability mailed December 13, 2013 at p. 2.

37. In my opinion, a POSA would not have understood the term "crystalline," as it is used in the claims of the patents-in-suit, to require that a composition contain only crystalline material. A POSA would understand that crystalline material can exist on its own or in a mixture of crystalline and non-crystalline materials. For example, if crystalline material is present in a pharmaceutical dosage form, even if that dosage form also contains other non-crystalline

material(s), the crystalline material itself is still crystalline, and the dosage form may still exhibit the properties of crystalline materials. For instance, if an active pharmaceutical ingredient (API) in a tablet is crystalline and other excipients are non-crystalline, the tablet as a whole would still exhibit X-ray diffraction peaks characteristic of the API's crystalline form. Similarly, if a solid API exists in the form of a mixture of crystalline and amorphous forms, a POSA would understand that the crystalline portion is still crystalline, and the mixture as a whole may exhibit crystalline properties. There also is nothing in the patents-in-suit or their prosecution histories that would indicate to a POSA that a material must be "entirely" crystalline to satisfy the claims.[2]

38. Furthermore, a POSA would understand that the term "crystalline" is a general descriptive term for solid forms, and is not limited to any particular form, such as the specific crystalline forms described in the patents-in-suits. As noted above, throughout the specification and prosecution histories of the patents-in-suits, this term is used consistently with its ordinary meaning. *See*, *e.g.*, '804 patent, col. 2, l. 39 to col. 3, l. 19; col. 11, ll. 34-36; col. 13, ll. 62-64; col. 14, ll. 29-32; File history of '921 patent, claims as filed September 19, 2013, at pp. 47-49; preliminary amendment filed September 19, 2013, at pp. 3-5; Notice of Allowability mailed December 13, 2013 at p. 2.

39. The specification does not suggest that the word "crystalline" itself should be limited to the specific forms the inventors identified. To the contrary, the specification explicitly refers to Forms I-XVI when such focus is intended. *See*, *e.g.*, '804 patent, col. 2, ll. 33-35.

40. An example of the claim term "crystalline modification" can be found in claim 1 of the '804 patent, which refers to "a compound which is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride anhydrate in *crystalline modification* IV

[2] Also, as a matter of logic, any amount of crystalline material (even if it makes up less than all of a compound or pharmaceutical composition) is itself necessarily "entirely" crystalline.

(Form IV)" (emphasis added). A POSA would understand that the claim term "crystalline modification" means "crystalline form." This interpretation is not only consistent with general usage in the field, but also supported by the specification of the patents-in-suits, which clearly states that "the term 'Form' is generally used as a synonym for the term 'modification.'" *See, e.g.*, '804 patent, col. 2, ll. 36-38.

B. "Exhibits the following XRD data"

Claim Term	Patent/claim	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"exhibits the following XRD data"	'020 patent, claim 1	Displays X-ray diffraction pattern consistent with the following values, with experimental error ranges (*e.g.*, +/- 0.1^{o} for two-theta values)	Must show all the following peaks and intensities

41. Claim 1 of the '020 patent recites, *inter alia*, "[a] compound which is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride anhydrate in crystalline modification IV (Form IV), wherein said compound *exhibits the following XRD data*" (emphasis added).

42. In my opinion, a POSA would interpret the term "exhibits the following XRD data" as used in claim 1 of the '020 patent as "displays X-ray diffraction pattern consistent with the following values, with experimental error ranges (*e.g.*, +/- 0.1^{o} for two-theta values)."

43. The result of every scientific experiment, including XRD experiments, has an error range. Thus, a POSA would interpret the two-theta values ("2θ"), interplanar spacing ("*d*") and relative intensity values ("I/I_0") presented in the table in claim 1 as having an experimental error range. This interpretation is supported by Table III of the specification of the patents-in-

suit, which provides XRD data corresponding to the data in claim 1 for vilazodone hydrochloride Form IV. '804 patent, col. 25, ll. 1-17. The header of Table III explicitly states that "[t]he XRD instrument is controlled for 2-theta ±0.1º. '804 patent, cols. 24-27, Table III. Furthermore, a POSA would understand that interplanar spacing (*"d")* is not measured directly, and instead is calculated from the measured two-theta values. Thus, the determined values of *d* will have an experimental variation as well. Similarly, a POSA would understand that experimentally determined relative intensity values ("I/I_0"), as referenced in the claims, also would be subject to experimental variation. *See*, further discussion of XRD peak intensities in paragraphs 49-52.

44. The prosecution history of the '020 patent is consistent with this interpretation of "exhibits the following XRD data." For instance, in the Amendment after Non-Final Rejection filed March 18, 2010, Applicants amended claim 1 to recite "wherein said compound exhibits the following XRD data," and stated in the accompanying remarks that "claim 1 is amended to recite the XRD data for Form IV as set forth at page 41 of the specification," *i.e.*, the Table III data for Form IV. Amendment after Non-Final Rejection filed March 18, 2010 at pp. 2-3 and 8. Because Table III of the specification expressly refers to an error range of +/-0.1^o for the two-theta values, as noted above, the prosecution history would further lead a POSA to understand that "exhibits the following XRD data" in claim 1 of the '020 patent includes experimental error ranges, *e.g.*, +/-0.1^o for the two-theta values.

C. "Corresponding to"

Claim Term	Patent/claim	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"corresponding to"	'804 patent, claims 1-3	Consistent with	Matching the precise values recited in the claims

45. The claims of the '804 patent refer to a compound "in crystalline modification IV (Form IV) having at least five characteristic peaks selected from the degrees two-theta values *corresponding to* 9.08±0.1, 12.85±0.1, 14.50±0.1, 16.89±0.1, 18.89±0.1, 20.43±0.1, 21.72±0.1, 24.61±0.1, 27.35±0.1 and 28.18±0.1" (emphasis added).

46. In my opinion, a POSA would understand that the term "corresponding to" in these claims means "consistent with."

47. A POSA would understand that the claimed characteristic peaks are determined experimentally, as set forth in the specification. *See*, '804 patent, Table III in col. 25; Figure 21. The POSA would understand further that like the result of every scientific measurement, the two-theta values determined by XRD experiments have an error range. It is a fundamental aspect in comparing two sets of experimental results, *e.g.*, results obtained by testing two different samples, to take into consideration the experimental error range. Here, the specification provided the error range information. *See*, *e.g.*, '804 patent, cols. 24-27, Table III (describing two-theta values with the experimental error range of +/- 0.1^{o}). Indeed, claims 1-3 of the '804 patent explicitly refer to this margin of error. The fact that the claims recite an error range shows that the two-theta values need not match precisely, but only be consistent with the stated error ranges, as a POSA would understand them and be able to compare results to them.

D. "Characteristic peak"

Claim Term	Patent/claim	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"characteristic peak"	'804 patent, claims 1-3	Peak representative of a crystalline form's X-ray diffraction pattern	A powder XRD peak having intensity ≥ 3*noise, which serves to

			identify the crystalline modification

48. The claims of the ‘804 patent refer to a compound “in crystalline modification IV (Form IV) having at least five *characteristic peaks* selected from the degrees two-theta values corresponding to 9.08±0.1, 12.85±0.1, 14.50±0.1, 16.89±0.1, 18.89±0.1, 20.43±0.1, 21.72±0.1, 24.61±0.1, 27.35±0.1 and 28.18±0.1” (emphasis added).

49. In my opinion, a POSA would understand the term “characteristic peak” as used in the claims of the ’804 patent to mean “peak representative of a crystalline form’s X-ray diffraction pattern.” A POSA would understand that characteristic peak(s) are those peak(s) in an XRD pattern that can be used to identify a particular crystalline form and distinguish it from other materials with confidence. A POSA would not impose any particular requirement regarding intensity level for a peak to be characteristic of a given crystalline form. Indeed, intensity of a peak is not an absolute property of a crystalline form, and could vary based on experimental conditions. A peak can have greater or lesser intensity, and still be identified as present and characteristic.

50. In particular, a POSA would not understand that a “characteristic peak” in an XRD pattern needs to have intensity $\geq$ 3*noise. If the POSA can observe XRD peak(s) sufficient to identify a particular form, such peak(s) are characteristic peak(s). Both intensity levels and noise levels can vary based on experimental conditions, so a POSA would not place an arbitrary intensity limit of 3*noise for identifying a characteristic peak. It is certainly possible for a POSA to identify a crystalline form using XRD peaks having intensities of less than 3*noise.

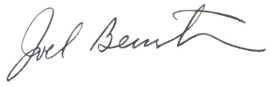
51. It would be an unrealistic criterion for the recognition of peaks as only those exceeding 3*noise. The 3*noise (or 3σ) level is a statistical measure of the level of confidence

in determining the presence of some observation or comparing two observations. That criterion derives from a normal distribution of the error, and the statistics are such that if the peak is 3*noise then it is said to be "observed at the 99% confidence level." The 2*noise (or 2σ) level is still determined with 90 % confidence, and the 1*noise (or 1σ) level is still determined with 68 % confidence. Having said that, determining a peak above background generally is not a matter of statistics, and a POSA is able to recognize a peak when he or she sees it, regardless of a specific n*noise level.

52. The header of Table III of the specification, "Data of powder-XRD-pattern of polymorphic Forms," states that "10 characteristic peaks of each polymorph have been taken for evaluation," and a footnote to Table III states that "Further peaks exhibit intensities ≤3*noise." *See*, '804 patent, col. 24, ll. 32-35; col. 25, ll. 2-5; col. 26, ll. 2-5; col. 27, ll. 2-5 and 11. The fact that the peaks listed in Table III had intensities ≥ 3*noise in the experiments reported in the specification would not suggest to a POSA that the term "characteristic peak" itself should be limited to peaks with intensities ≥ 3*noise. To the contrary, the Table III peaks would still be just as characteristic of the identified crystalline forms whether or not they were present with intensity ≥ 3*noise in a given experiment. For example, a POSA would still be able to observe these peaks in an experiment with a higher noise level. Furthermore, by stating in a footnote that "[f]urther peaks exhibit intensities ≤3*noise," Table III of the specification specifically contemplates the existence of other characteristic peaks with intensities less than 3*noise that are observable and recognizable by a POSA. '804 patent, col. 27, footnote to Table III.

53. I reserve the right to amend or supplement my declaration in the event that additional documents and/or information are brought to my attention.

I declare under penalty of perjury that the foregoing is true and correct to the best of my own personal knowledge.



Dated: June 21, 2016

Joel Bernstein, Ph.D.